PATENT
Docket No.: **29556.0001 (SU-1976)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Goldman et al.	Examiner: R. Hutson
Serial No.	:	09/282,239	Art Unit: 1652
Cnfrm. No.	:	8339	
Filed	:	March 31, 1999	
For	:	A METHOD FOR ISOLATING AND PURIFYING OLIGODENDROCYTES AND OLIGODENDROCYTE PROGENITOR CELLS	

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 CFR § 41.37, appellants hereby file their appeal brief. Enclosed is the filing fee of $270.00 required by 37 CFR § 41.20(b)(2) and the $1,175.00 fee for a 5-month extension of time pursuant to 37 CFR §§ 41.37(e), 1.136(a), and 1.17(a) . You are hereby authorized to charge/credit Account No. 50-5409 for any deficiency/overage.

I. REAL PARTY IN INTEREST

The owner of the present application is Cornell Research Foundation, Inc., pursuant to an assignment, recorded on May 25, 1999, at Reel 009985, Frame 0315. In accordance with

an inter-institutional agreement, the University of Rochester also has rights in the present application.

II. RELATED APPEALS AND INTERFERENCES

A prior Notice of Appeal to the Board of Patent Appeals and Interferences ("Board") in the present application was filed on January 12, 2006. It was withdrawn as a result of the filing of a request for continued examination. Beyond that, there are no related appeals or interferences.

III. STATUS OF CLAIMS

A. Claims 25, 26, and 29-44 Are Finally Rejected

Claims 42-44 have been finally rejected under 35 U.S.C. § 112, as failing to comply with the written description requirement.

Claims 25, 26, and 29-41 have been finally rejected under 35 U.S.C. § 102(e), as being anticipated by, or, under 35 U.S.C. § 103(a), for obviousness over U.S. Patent No. 6,361,996 B1 to Rao et al. ("the '996 patent").

B. Claims 1-24, 27-28, and 45 Have Been Canceled

Claims 1-24, 27-28, and 45 have been canceled.

C. No Claims Stand Allowed

No claims stand allowed.

D. Claims 25, 26, 29-44 Are On Appeal

The decision of the examiner finally rejecting claims 25, 26, and 29-44 is appealed. These claims, in their current pending form, are set forth in the attached Claims Appendix.

IV. STATUS OF AMENDMENTS

No amendment was filed after final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 25 of the present application is directed to an enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, (U.S. Patent Application Serial No. 09/282,239 ("present application"), p.4, ll 8-9; p.9, ll 20-22; Example 4; p.22, ll 6-10; originally-filed claim 17; and Figure 4, showing maturation of oligodendrocyte progenitor cells to oligodendrocytes, of the present application), where the majority of cells in the enriched or purified preparation differentiate into O4 positive oligodendrocytes (present application, p.8, ll 24-25; p.17, ll 31-32; p.18, ll 1-8; p.19, ll 17-19; p.21, ll 16-25; and Figure 4), and where, when cultured in PDGF, FGF2, and NT3, further develop into galactocerebroside positive oligodendrocytes in the presence of 5% FBS/IGF-1 (present application, p.8, ll 4-8; p.21, ll 1-19, ll 24-28; p.23, ll 23-26; and Figures 4 and 7F, showing maturation of oligodendrocyte progenitor cells to GalC (i.e. galactocerebroside) positive oligodendrocytes). In this enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, the mitotic oligodendrocyte progenitor cells are from a post-natal human (present application, p.13, ll 30-31; p.14, ll 24-28; p.18 ll 29-33; p.19, ll 1-28, and Example 4), and a human cyclic nucleotide phosphodiesterase gene P2 promoter is transcriptionally active in the oligodendrocyte progenitor cells (present application, p.5, ll 1-3, ll 17-22; and p.20, ll 1-20).

Claim 26 of the present application is directed to an enriched or purified preparation of human mitotic oligodendrocyte progenitor cells (present application, p.4, ll 8-9; p.9, ll 20-22; Example 4; p.22, ll 6-10; originally-filed claim 17; and Figure 4, showing maturation of oligodendrocyte progenitor cells to oligodendrocytes), where the majority of cells in the

enriched or purified preparation differentiate into O4 positive oligodendrocytes (present application, p.8, ll 24-25; p.17, ll 31-32; p.18, ll 1-8; p.19, ll 17-19; p.21, ll 16-25; and Figure 4), and where, when cultured in PDGF, FGF2, and NT3, further develop into galactocerebroside positive oligodendrocytes in the presence of 5% FBS/IGF-1 (present application, p.8, ll 4-8; p.21, ll 1-19, ll 24-28; p.23, ll 23-26; and Figures 4 and 7F, showing maturation of oligodendrocyte progenitor cells to GalC (i.e. galactocerebroside) positive oligodendrocytes). In this enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, the mitotic oligodendroctye progenitor cells are from an adult human (present application, p.13, ll 30-32; p.18 ll 29-32; p.19, ll 1-8; Example 4; and Figures 2A-I, showing that adult human white matter harbors oligodendrocyte progenitors), and a human cyclic nucleotide phosphodiesterase gene P2 promoter is transcriptionally active in the oligodendrocyte progenitor cells (present application, p.5, ll 1-3, ll 17-22; and p.20, ll 1-20).

Claim 29 of the present application is directed to an enriched or purified preparation of human mitotic oligodendrocyte progenitor cells (present application, p.4, ll 8-9; p.9, ll 20-22; Example 4; p.22, ll 6-10; originally-filed claim 17; and Figure 4, showing maturation of oligodendrocyte progenitor cells to oligodendrocytes), where the majority of cells in the enriched or purified preparation differentiate into O4 positive oligodendrocytes (present application, p.8, ll 24-25; p.17, ll 31-32; p.18, ll 1-8; p.19, ll 17-19; p.21, ll 16-25; and Figure 4), and where, when these enriched or purified preparation of human mitotic oligodendrocyte progenitor cells are cultured in PDGF, FGF2, and NT3, they further develop into galactocerebroside positive oligodendrocytes in the presence of 5% FBS/IGF-1 (present application, p.8, ll 4-8, ll 24-25; p.21, ll 16-28; p.23, ll 23-26; and Figures 4 and 7F, showing maturation of oligodendrocyte progenitor cells to GalC (i.e. galactocerebroside) positive

oligodendrocytes). In claim 29, the oligodendrocyte progenitor cells express A2B5 antigen and do not express O4 antigen (present application, Example 5; and p.21, ll 1-19).

Claim 30 of the present application is directed to an enriched or purified preparation of human mitotic oligodendrocyte progenitor cells (present application, p.4, ll 8-9; p.9, ll 20-22; Example 4; p.22, ll 6-10; originally-filed claim 17; and Figure 4, showing maturation of oligodendrocyte progenitor cells to oligodendrocytes), where the majority of cells in the enriched or purified preparation differentiate into O4 positive oligodendrocytes (present application, p.8, ll 24-25; p.17, ll 31-32; p.18, ll 1-8; p.19, ll 17-19; p.21, ll 16-25; and Figure 4), and where, when cultured in PDGF, FGF2, and NT3, the cells further develop into galactocerebroside positive oligodendrocytes in the presence of 5% FBS/IGF-1 (present application, p.8, ll 4-8, ll 24-25; p.21, ll 16-25, ll 24-28; p.23, ll 23-26; and Figures 4 and 7F, showing maturation of oligodendrocyte progenitor cells to GalC (i.e. galactocerebroside) positive oligodendrocytes). In this enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, the mitotic oligodendrocyte progenitor cells are from a fetal human (present application, p.13, ll 30-32; and p.14, ll 24-28) and a human cyclic nucleotide phosphodiesterase gene P2 promoter is transcriptionally active in the oligodendrocyte progenitor cells (present application, p.5, ll 1-3, ll 6-8, ll 17-22; and p.20, ll 1-20).

Claim 42 of the present application is directed to the enriched or purified preparation of claim 25, where 66.3 ± 6.8% of cells in the enriched or purified preparation mature into O4-IR oligodendrocytes when cultured in the presence of 5% FBS/IGF-1 (present application, p.17, ll 15-24; p.19, ll 17-19; p.21, ll 24-28; and Figures 4 and 7F, showing maturation of oligodendrocyte progenitor cells to GalC (i.e. galactocerebroside) positive oligodendrocytes).

Claim 43 of the present application is directed to the enriched or purified preparation of claim 26, where 66.3 ± 6.8% of cells in the enriched or purified preparation mature into O4-IR oligodendrocytes when cultured in the presence of 5% FBS/IGF-1 (present application, p.17, ll 15-24; p.19, ll 17-19; p.21, ll 24-28; and Figures 4 and 7F, showing maturation of oligodendrocyte progenitor cells to GalC (i.e. galactocerebroside) positive oligodendrocytes).

Claim 44 of the present application is directed to the enriched or purified preparation of claim 29, where 66.3 ± 6.8% of cells in the enriched or purified preparation mature into O4-IR oligodendrocytes when cultured in the presence of 5% FBS/IGF-1 (present application, p.17, ll 15-24; p.19, ll 17-19; p.21, ll 24-28; and Figures 4 and 7F, showing maturation of oligodendrocyte progenitor cells to GalC (i.e. galactocerebroside) positive oligodendrocytes).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(1) Rejection of claims 42-44 as failing to comply with the written description requirement of the first paragraph of 35 U.S.C. § 112.

(2) Rejection of claims 25, 26, and 29-41, under 35 U.S.C. § 102(e), as being anticipated by or, under 35 U.S.C. § 103(a), for obviousness over the '996 patent.

VII. ARGUMENT

A. The Claimed Invention Complies With the Written Description Requirement

The final office action, mailed December 23, 2009 ("Final Office Action"), states that the claims 42-45 are rejected under 35 U.S.C. § 112 (1st para.), as failing to comply with the written description requirement (Final Office Action, p.2, ll 10-20). The basis for this rejection is that the phrase "66.3 ± 6.8% of cells in the enriched or purified preparation

mature into O4-IR oligodendrocytes" lacks support in the original disclosure of the present application because Example 6 only mentions O4-IR cells -- not O4-IR oligodendrocytes (*id.*, ll 20-23). We disagree.

Example 6 is entitled "P/hCNP2:hGFP^{+} -sorted Cells Matured Largely, but not Exclusively, into **Oligodendrocytes**" (emphasis added). This concept is repeated in the first sentence of this example which states that "[t]he majority of CNP2-sorted cells developed and matured as **oligodendrocytes**" (emphasis in original). As to these sorted cells, the next sentence of Example 6 specifies that "[b]y 3 weeks after FACS [(i.e. fluorescence-activated cell sorting)], 74.1 ± 7.7% of **these cells** expressed oligodendrocytic CNP protein; a matched sample of **sorted cells** stained after 3 weeks *in vitro* for O4 yielded 66.3 ± 6.8% O4-IR **cells** (emphasis added). As explained in the present application oligodendrocytes are O4 positive (*see* present application, Figure 4 and p.19, ll 17-19). Thus, read in context, the phrase "66.3 ± 6.8% of cells in the enriched or purified preparation mature into O4-IR oligodendrocytes" in Example 6 is clearly referring to O4-IR oligodendrocytes as set forth in claims 41-44. This argument was presented on September 10, 2009, p.5, ll 2-6.

Thus, the rejection of claims 42-45 under 35 U.S.C. § 112 (1st para.) is improper and should be withdrawn.

B. The '996 Patent Does Not Anticipate or Render Obvious the Claimed Invention

1. <u>Background of Present Invention</u>

The background of the present invention applies as of the time the present application was filed.

A major impediment to both the analysis of the biology of adult neural precursors, and to their use in engraftment and transplantation studies, has been their relative scarcity in adult brain tissue, and their consequent low yield when harvested by enzymatic dissociation

and purification techniques (present application, p.2, ll 9-12). As a result, attempts at either manipulating single adult-derived precursors or enriching them for therapeutic replacement have been difficult (*id.*, ll 12-14).

The repair of damaged brain requires not only sources of new neurons but also new glial support cells (present application, p.3, ll 4-5). Oligodendrocytes are the glial cell type that produce myelin and insulate neuronal axons by ensheathment with myelin-bearing cell processes (*id.*, ll 5-7). Like neurons, oligodendrocytes are largely postmitotic and cannot regenerate through proliferative expansion (*id.*, ll 7-8). However, persistent oligodendrocyte progenitors have been described in adult rodent subcortical white matter, and may provide a substrate for remyelination after demyelinating injury (*id.*, ll 8-11). In humans, the demonstration and identification of analogous subcortical oligodendrocyte progenitor cells has been problematic (*id.*, ll 11-12). A pre-oligodendrocytic phenotype has been described in adult human subcortical white matter, though these postmitotic cells may have included mature oligodendrocytes recapitulating their developmental program after dissociation (*id.*, ll 12-15). Rare examples of oligodendrocytes derived from mitotic division have also been reported in human subcortical dissociates, but the identification and isolation of their mitotic progenitors have proven elusive (*id.*, ll 16-18). As a result, the enrichment of these cells for functional utilization has proven difficult (*id.*, ll 18-19). In particular, the cells have not been preparable in the numbers or purity required for *in vivo* engraftment into demyelinated recipient brain, whether experimentally or for clinical therapeutic purposes (*id.*, ll 19-22).

A strong need therefore exists for a new strategy for identifying, separating, isolating and purifying native oligodendrocyte precursor cells from brain tissue (*id.*, ll 23-25). Such isolated, enriched native precursors may be used in engraftment and transplantation in

demyelinating disorders, as well as for studies of growth control and functional integration (*id.*, ll 25-27).

2. The Present Invention

The present invention is directed to overcoming the above-noted problems in the art by providing an enriched purified population of oligodendrocyte progenitor cells.

Prior approaches toward the use of neural precursor cells have focused upon preparing clonal lines derived from single progenitors (present application, p.4, ll 26-27). However, such propagated lines can become progressively less representative of their parental precursors with time and passage *in vitro* (*id.*, ll 27-29). To circumvent these difficulties, the present invention provides for an enriched purified population of oligodendrocyte progenitor cells (*see id.*, ll 29-32; p.5, ll 1-3).

By providing enriched and purified oligodendrocytic progenitor cells, from adult and fetal brain, the present invention may significantly accelerate the study of precursor and stem cell biology (*see id.*, p.6, ll 23-25). In particular, it may allow the preparation and enrichment of oligodendrocytic and other neural precursor cells in sufficient number to permit implantation and engraftment using native, unpassaged adult-derived progenitor cells (*id.*, ll 25-28). It may spur the development of induced adult oligoneogenesis as a viable therapeutic modality for the structural repair of damaged or demyelinated central nervous system (*id.*, ll 28-31). The potential use of these cells as substrates for induced remyelination suggests therapeutic strategies appropriate to a variety of white matter diseases (*id.*, ll 31-32; p.7, ll 1-5).

3. U.S. Patent No. 6,361,996 to Rao et al. ("'996 patent")

The '996 patent discloses multipotential neuroepithelial stem cells and lineage-restricted oligodendrocyte-astrocyte precursor cells ('996 patent Abstract). The

oligodendrocyte-astrocyte precursor cells are derived from neuroepithelial stem cells, are capable of self-renewal, and can differentiate into astrocytes and oligodendrocytes but not neurons (*id.*). The '996 patent characterizes these cells as "**multipotential** intermediate precursor cells restricted to glial lineages" (emphasis added) ('996 patent col. 23, ll 1-5).

Figure 1 of the '996 patent and the supporting text of the specification refer to cell type 14 as a multipotential precursor cell that can generate oligodendrocytes 18 and astrocytes 22 (*see id.*, col. 6, ll 60-64 and Figure 1, below).

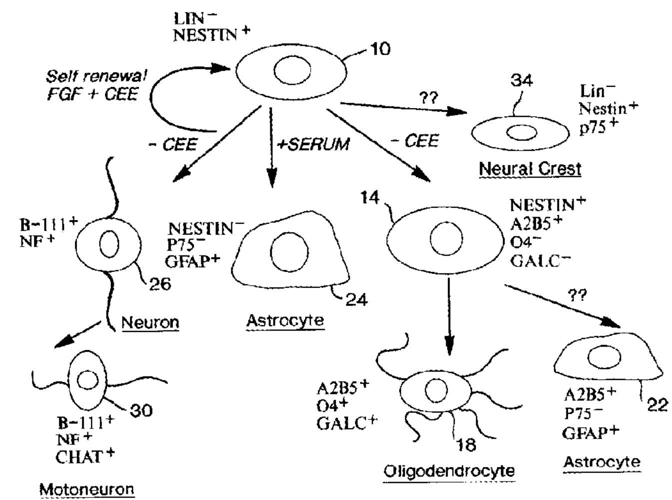

FIG. 1

Cell type 14 is said to be generated from embryonic spinal cord stem cells (*id.*, col. 6, ll 35-64). Figure 2 of the '996 patent depicts multipotent neuroepithelial stem cells 50 which differentiate into oligodendrocyte-astrocyte progenitor cells 54 that are capable of self-renewal as well as further differentiating into oligodendrocytes 58, type 1 astrocytes 62, and type 2 astrocytes 66 (*id.*, col. 17, ll 4-9). *See* Figure 2, below.

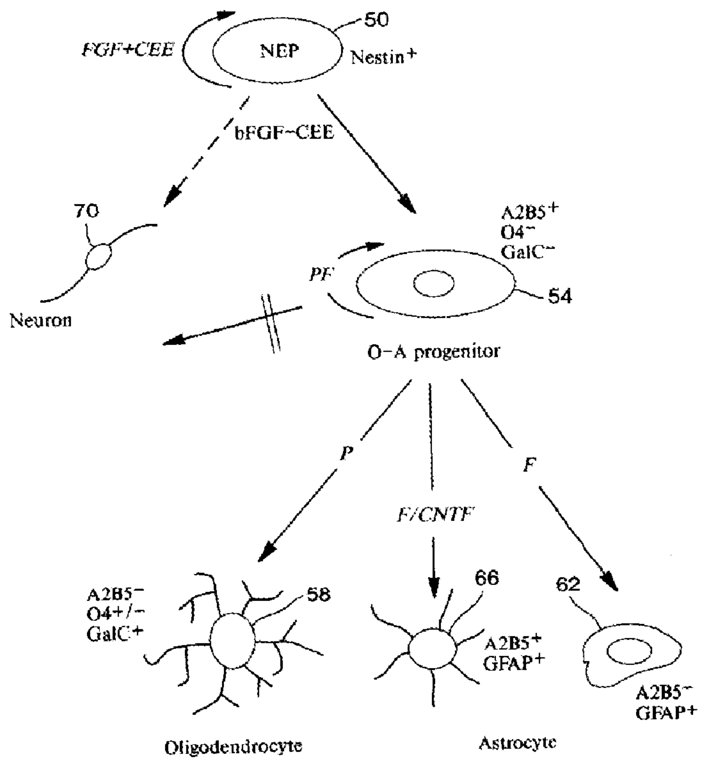

FIG. 2

Examples 14 and 15 of the '996 patent demonstrate that the oligodendrocyte-astrocyte precursor cells have strong bias to differentiate to astrocytes. In particular, Example 14, col. 20, ll 44-60 states:

> After 5 days of culturing NEP cells in the absence of CEE, cells were immunopurified, plated on fibronectin/laminin coated dishes, and exposed to cytokines previously associated with differentiation of precursor into oligodendrocytes, astrocytes, or neurons. The A2B5-panned population was >98% positive of A2B5$^+$ cells when stained one hour after panning. Staining 24 hours after plating showed that all cells of the panned population were

A2B5$^+$ and did not express any other lineage markers tested.

Panned cultures in the presence of bFGF and no other growth factors for 5 days consisted of 1% oligodendrocytes, 50% GFAP$^+$ astrocytes, and 49% A2B5$^+$ cells. The proportion of differentiated cells was significantly shifted when the bFGF-containing medium was replaced after 3 days with medium supplemented only with PDGF. Under these conditions, the culture consisted of 30% oligodendrocytes, 50% astrocytes, and 20% A2B5$^+$ cells.

Similarly, Example 15 of the '996 patent (col. 21, l 59 to col. 22, l 11) states that as a result of culturing in CNTF and bFGF, the A2B5$^+$ cells predominantly differentiate into cells with a type-2 astrocyte phenotype.

4. <u>The '996 Patent Does Not Explicitly Anticipate the Claimed Invention</u>

35 U.S.C. § 102(e) imposes the requirement that a claimed invention, to be patentable, must not have been "described in . . . a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent." To be anticipatory, under 35 U.S.C. § 102, a single prior art reference must disclose, either expressly or inherently, each limitation of the claim. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992). This argument was presented in the prior appeal brief, p.3, ll 26-32.

a). The '996 Patent Does Not Disclose Oligodendrocyte Progenitor Cells, A Majority of Which Differentiate to O4 Positive Oligodendrocytes

In the final office action, the examiner identified Figure 1 of the '996 patent in support of the rejection of claims 25, 26, and 29-41 under 35 U.S.C. § 102(e) (*see* Final

Office Action, p.4, ll 4-13) and the supporting text regarding cell type 14. As this figure and the paragraph bridging columns 6 and 7 of the '996 patent make clear, cell type 14 is a multipotential precursor cell that can generate oligodendrocytes 18 and astrocytes 22. Cell type 14 is said to be generated from embryonic spinal cord stem cells. None of cells 14, 18, and 22 constitute the claimed enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, where the majority of cells in that preparation differentiate into O4 positive oligodendrocytes. Multipotential precursor cells 14 differentiate mostly to astrocytes, while oligodendrocytes 18 and astrocytes 22 are in a completely differentiated form. The same is true for oligodendrocyte-astrocyte progenitors 54, oligodendrocytes 58, and astrocytes 62 and 66 in Figure 2. Further, as noted *supra*, Examples 14 and 15 of the '996 patent teach that the majority of the multipotential precursor cells differentiate to astrocytes.

The bias of the '996 patent's oligodendroctye-astrocyte progenitors to differentiate to astrocytes clearly distinguishes them from the presently claimed oligodendrocyte progenitor cells, the majority of which mature into oligodendrocytes.

As described *supra*, the only relevant undifferentiated cells disclosed by the '996 patent are multipotential neuroepithelial stem cells and lineage-restricted oligodendrocyte-astrocyte precursor cells. This is entirely consistent with the previously-submitted Declaration of Mahendra S. Rao, M.D., Ph.D. under 37 C.F.R. § 1.132 ("First Rao Declaration") (Evidence Appendix Exhibit 1) and Second Declaration of Mahendra S. Rao, M.D., Ph.D. under 37 C.F.R. § 1.132 ("Second Rao Declaration") ¶ 6 (Evidence Appendix Exhibit 2).

Declarant Mahendra S. Rao ("Dr. Rao"), the same Dr. Rao who is the first-named inventor of the '996 patent, has stated that the '996 patent's oligodendrocyte-astrocyte

precursor cells are in a less differentiated state than the oligodendrocyte progenitor cells claimed in the present application (*id.*). Gregori et al., "The Tripotential Glial-Restricted Precursor (GRP) Cell and Glial Development in the Spinal Cord: Generation of Bipotential Oligodendrocyte-Type-2 Astrocyte Progenitor Cells and Dorsal-Ventral Differences in GRP Cell Function," *J. Neurosci.* 22(1):248-256 (2002) (Evidence Appendix Exhibit 3) has suggested that the '996 patent describes a glial progenitor that gives rise to a more restricted astrocyte/oligodendrocyte precursor that still directly makes predominantly astrocytes and a small minority of oligodendrocytes (Second Rao Declaration ¶ 7). Thus, cells in the '996 patent's pathway to oligodendrocyte production are bi-potential astrocyte/oligodendrocyte progenitor cells that have strong astrocytic bias (*id.*). The bias of the '996 patent's oligodendroctye-astrocyte progenitor to differentiate to astrocytes clearly distinguishes them from the presently claimed oligodendrocyte progenitor cells, the majority of which mature into oligodendrocytes.

Appellants presented this argument in amendments filed on March 28, 2007, p.5, ll 12-26; December 7, 2007, p.6, ll 27-41; March 14, 2008, p.6, ll 25-40, p.7, ll 1-2; October 27, 2008, p.6, ll 23-40; and September 10, 2009, p.6, ll 20-36.

b). The '996 Patent Does Not Work With Human Oligodendrocyte Progenitor Cells

While noting that the '996 patent's experimental work was with rat cells, the Final Office Action states that human stem cells could likewise be isolated and, presumably used to produce human multipotential precursors of both oligodendrocytes and astrocytes (Final Office Action, p.4, ll 1-13). The examiner further notes that mammalian neuroepithelial stem cells can be isolated from human and non-human primates, equines, canines, felines, bovines, porcines, ovines, lagomorphs, and the like (*id.*). The examiner asserts that the preparation taught by the '996 patent is such that a cyclic nucleotide phosphodiesterase 2 promoter is

transcriptionally active in all cells of the enriched or purified preparation (*id.*, ll 14-21). Therefore, the examiner asserts, that one of ordinary skill in the art would have been motivated to use the methods taught by the '996 patent to isolate an enriched or purified preparation of human mitotic oligodendrocyte progenitor cells from humans so that these pure cell preparations could be used to treat neurological disorders in humans (*id.*, p.5, ll 11-21; p.6, ll 1-2).

However, no where does the '996 patent recover the claimed cell population (where a majority of the population differentiate into O4 positive oligodendrocytes) from rats, let alone humans. The examiner asserts that those skilled in the art would have the desire to find such human oligodendrocyte progenitor cells. However, even with such a desire, there is no reason to believe that it is achievable where the '996 patent does not teach the claimed cells in rats or humans. In view of the '996 patent's failure to produce rat cells where a majority of those cells differentiate into O4 positive oligodendrocytes, there can be no expectation of success in producing human cells with that capability. This argument was presented in amendments filed on October 27, 2008, p.7, ll 23-26 and September 10, 2009, p.7, ll 23-32.

There are fundamental differences between the biology of rat and human oligodendrocyte progenitor cells even if the '996 patent disclosed such rat cells which it does not (*see* Declaration of Steven A. Goldman under 37 C.F.R. § 1.132 ("First Goldman Declaration") ¶ 7 (Evidence Appendix Exhibit 4)).[1] Furthermore, there are fundamental differences between the lineage restriction and potential of neonatal and adult oligodendrocyte progenitor cells (Noble et al., "The O2A (Adult) Progenitor Cell: A Glial

1 Although the First Goldman Declaration was directed to U.S. Patent No. 5,276,145 to Bottenstein, the issues regarding that reference are substantially the same as those pertaining to the '996 patent.

Stem Cell of the Adult Central Nervous System," *Seminars in Cell Biol.* 3:413-22 (1992) (Evidence Appendix Exhibit 5); Windrem et al., "Fetal and Adult Human Oligodendrocyte Progenitor Cell Isolates Myelinate the Congenitally Dysmyelinated Brain," *Nature Medicine* 10:93-97 (2004) (Evidence Appendix Exhibit 6) ("Windrem 2004"); and Third Declaration of Steven A. Goldman under 37 C.F.R. § 1.132 ("Third Goldman Declaration") ¶ 6 (Evidence Appendix Exhibit 7)). These biological differences between both rat and human and perinatal and adult progenitor cells were not recognized by the '996 patent, whose cells were restricted to neonatal rodent derivation (First Goldman Declaration ¶ 7; Third Goldman Declaration ¶ 6). Whereas rat oligodendrocytes appear to retain mitotic potential, human oligodendrocytes do not (Third Goldman Declaration ¶ 7). *See* Kirschenbaum et al., "*In Vitro* Neuronal Production and Differentiation by Precursor Cells Derived from the Adult Human Forebrain," *Cerebral Cortex* 6:576-89 (1994) (Evidence Appendix Exhibit 8). As a result, the oligodendrocyte progenitor cells of the rat brain cannot be considered homologous to its human counterpart (First Goldman Declaration ¶ 7). In particular, methods that permit the selective extraction and/or growth of oligodendrocyte progenitors from the rat brain do not differentiate between oligodendrocyte progenitor cells and mature oligodendrocytes able to re-enter the mitotic cycle (*id.*). In humans, these constitute two discrete phenotypes, lineally related but temporally distinct (*id.*). The present invention teaches the selective acquisition of a highly enriched-to virtual purity-mitotically-competent oligodendrocyte progenitor cell pool, operationally separate and distinct from post-mitotic or mature oligodendrocytes (*id.*).

Figures 1 and 2 of the '996 patent show the astrocyte/oligodendrocyte precursor cells differentiating directly to astrocytes and, to a much lesser extent, to oligodendrocytes with these mature cell types being characterized by various markers. It may be accurate to

characterize rat oligodendrocytes and oligodendrocyte progenitors together at least with regard to their markers, because those markers are similar. Specifically, rat oligodendrocyte progenitors and oligodendrocytes both express the antigenic marker recognized by monoclonal antibody O4 (Third Goldman Declaration ¶ 7). In contrast, this marker is expressed by human oligodendrocytes and their immature forms, but NOT by mitotic oligodendrocyte progenitor cells (*id.*). As a result, human oligodendrocyte progenitor cells cannot be acquired through the use of O4 as a selection marker, and O4-defined human oligodendroglial cells cannot act as mitotically-competent progenitor cells (*id.*). This is in sharp distinction to the rat brain, in which the use of this marker can identify oligodendrocyte progenitors (*id.*). The '996 patent does not recognize the non-applicability of this marker to the separation of human oligodendrocyte progenitor cells (*id.*). In humans, mitotic cells biased strongly towards the oligodendrocyte lineage are instead recognized by the antigenic phenotype $O4^-$/PSA-$NCAM^-$/$A2B5^+$, which comprise a distinct subpopulation in which the CNP2 (i.e. cyclic nucleotide phosphodiesterase 2) promoter is transcriptionally activated (*id.*).

As a result of these considerations, the selective propagation of mitotically-active oligodendrocyte progenitor cells from the rat brain does not predict the successful isolation of mitotic oligodendrocyte progenitor cells from postnatal or adult human brain tissue.

In view of all the foregoing, it is apparent that there is no evidence to support a position that the '996 patent explicitly anticipates the claimed invention.

Appellants presented this argument in the prior appeal brief, p.11, ll 10-31.

5. <u>The '996 Patent Does Not Inherently Anticipate the Claimed Invention</u>

Having demonstrated that the '996 patent does not explicitly anticipate the invention of claims 25, 26, and 29-41, the only basis for rejection under 35 U.S.C. § 102 is under the

doctrine of inherency. The Final Office Action (p.10, ll 6-15) states that the claims are anticipated by Examples 7 and 15 of the '996 patent. According to the examiner, these examples must produce an intermediate between the '996 patent's oligodendrocyte-astrocyte precursor cells and fully differentiated cells (*id.*). The examiner particularly relies on Example 7's mention of cells that appeared to have a different morphology than the oligodendrocyte type-2 astrocyte progenitors or mature oligodendrocytes in asserting anticipation (*id.*). Appellants disagree.

"Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295, 63 USPQ2d 1597, 1599 (Fed. Cir. 2002) (quoting *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). In order for an element, not expressly disclosed in a prior art reference, to inherently anticipate, the missing element must be "necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

When a prior art rejection is based on the inherent characteristics of a claimed product, as disclosed in the cited art, the examiner's burden for maintaining the rejection, and appellants' burden in rebutting this rejection, is well-defined. "[W]hen the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada,* 911 F.2d 705, 708, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Evidence that "the PTO did not correctly apply or understand the subject matter of the reference, or [that] the PTO drew unwarranted conclusions therefrom" will provide an adequate rebuttal. *Id*. The final office action makes no effort to satisfy this standard.

Firstly, Examples 7 and 15 of the '996 patent involve work with rat -- not human -- cells. Therefore, it is not seen how these examples could have any inherent disclosure of the claimed human mitotic oligodendrocyte progenitor cells.

Secondly, the mention, in Example 7, ll 13-24 of the '996 patent, of cells having a flattened morphology that is different than the oligodendrocyte type-2 astrocyte progenitors or mature oligodendrocytes does not mean that those additional cells are the claimed oligodendrocyte progenitor cells. There is no evidence whatsoever that the more mature looking oligodendrocytes referred to in this passage of the '996 patent were produced as a result of differentiation of these flattened cells instead of the oligodendrocyte-astrocyte precursors 14 in accordance with Figure 1 of the '996 patent. The examiner's position to the contrary is entirely speculative and is contrary to what Dr. Rao said in his second declaration. In taking this position, the examiner is impermissibly ignoring the testimony of Dr. Rao who is in a far better position to know what cell types his work made and did not make. The examiner's suggestion in the Final Office Action (p.9) that he is in a better position than Dr. Rao to engage in "considering exactly what Dr. Rao is testifying to and considering this in light of the evidence based upon the teaching[s] of [the '996 patent]" lacks any validity. Dr. Rao is an expert in the art who did the work in question -- not the examiner.

The fact that mature oligodendrocytes were present does not support the examiner's position. There is no evidence to suggest that these are oligodendrocyte progenitor cells, the majority of which differentiate into oligodendrocytes; to the contrary, they do not have the typical morphology that would be expected of oligodendrocyte progenitors under these culture conditions. One of ordinary skill in the art would have expected that the oligodendrocyte type-2 astrocyte progenitors of the '996 patent, having an astrocyte bias, would differentiate into astrocytes. Even if there was an intermediate between the

’996 patent’s oligodendrocyte type 2-astrocyte progenitors and mature astrocytes, such intermediate cells would similarly differentiate to astrocytes unlike the oligodendrocyte progenitors of the present invention. This argument was presented in amendments filed on October 27, 2008, p.7, ll 23-32 and September 10, 2009, p.7, ll 23-32 to p.8, ll 1-12 .

It is important to note that multiple pathways to generate post-mitotic, mature oligodendrocytes, have been described (Second Rao Declaration ¶ 7). Anderson and colleagues have shown that an oligodendrocyte/motor neuron precursor exists that does not make astrocytes (Zhou et al., “The bHLH Transcription Factors OLIG2 and OLIG1 Couple Neuronal and Glial Subtype Specification,” *Cell* 109:61-73 (2002) (Evidence Appendix Exhibit 9)) (*id.*). Other investigators have shown distinct sites of origin of oligodendrocytes and astrocytes presumably from separate precursors (Vallstedt et al., “Multiple Dorsoventral Origins of Oligodendrocyte Generation in the Spinal Cord and Hindbrain,” *Neuron* 45:55-67 (2005) (Evidence Appendix Exhibit 10); Cai et al., “Generation of Oligodendrocyte Precursor Cells from Mouse Dorsal Spinal Cord Independent of *Nkx6* Regulation and *Shh* Signaling,” *Neuron* 45:41-53 (2005) (Evidence Appendix Exhibit 11); and Second Rao Declaration ¶ 7). Yet other investigators have shown that different kinds of oligodendrocyte progenitors exist (Pringle et al., “*Fgfr3* Expression by Astrocytes and Their Precursors: Evidence that Astrocytes and Oligodendrocytes Originate in Distinct Neuroepithelial Domains,” *Development* 130:93-102 (2003) (Evidence Appendix Exhibit 12); and Second Rao Declaration ¶ 7). Since the state of the art suggests that different oligodendrocyte-astrocyte cell profiles exist in different circumstances, there is no reason to believe, as the examiner has suggested, that the ’996 patent inherently produces another precursor which has the claimed characteristics -- an enriched or purified preparation human mitotic oligodendrocyte

progenitor cells, where the majority of cells in the enriched or purified preparation differentiate into O4 positive oligodendrocytes.

This argument was presented in amendments filed on March 28, 2007, p.5, ll 27-37, p.6, ll 1-6; December 7, 2007, p.7, ll 3-19; March 14, 2008, p.7, ll 3-19; October 27, 2008, p.7, ll 1-17; and September 10, 2009, p.6, ll 36-38, p.7, ll 1-16.

In view of the foregoing, the ’996 patent cannot inherently anticipate the claimed invention.

6. Claims 26 and 42-45 are Patentable of Their Own Accord

a). Claim 26

Appellants maintain that claim 26 is patentable of its own accord, because the claimed adult human oligodendrocyte progenitor cells are distinguishable from the ’996 patent’s glial progenitor cells from newborn rat brain. The examiner’s suggestion that this difference in age is not a proper basis for distinguishing the claimed invention is unsupported and completely incorrect. Those skilled in the art would readily recognize that the difference in lineage between the ’996 patent’s newborn rat cells and the adult human cells of claim 26 constitutes a clear distinction in the cells’ stage of development. Simply put, oligodendrocyte progenitor cells from adults and newborns are not the same. *See* Windrem 2004. In view of this significant difference, the ’996 patent cannot be said to teach or suggest the cells of claim 26. This argument was presented in amendments filed on March 28, 2007, p.6, ll 19-26; December 7, 2007, p.7, ll 32-34, p.8 ll 1-5; March 14, 2008, p.7, ll 32-34, p.8, ll 1-5; October 27, 2008, p.8, ll 1-8; and September 10, 2009, p.8, ll 13-23.

The ’996 patent is directed to the enrichment of glial progenitor cells from newborn rat brain (First Rao Declaration ¶ 8). Newborns have an abundant population of still-developing oligodendrocyte progenitor cells that may constitute a significant fraction of all of

the cells in neonatal brain tissue (*id.*). Yakovlev et al., "A Stochastic Model of Brain Cell Differentiation in Tissue Culture," *J. Math. Biol.* 37(1):49-60 (1998) (Evidence Appendix Exhibit 13); Bögler et al., "Measurement of Time in Oligodendrocyte-Type-2 Astrocyte (O-2A) Progenitors is a Cellular Process Distinct from Differentiation or Division," *Dev. Biol.* 162(2):525-38 (1994) (Evidence Appendix Exhibit 14); and Raff et al., "Platelet-derived Growth Factor from Astrocytes Drives the Clock that Times Oligodendrocyte Development in Culture," *Nature* 333:562-65 (1988) (Evidence Appendix Exhibit 15) ("Raff 1988") describe cell cycle changes as glial progenitor cells mature (First Rao Declaration ¶ 8). They showed that adult cells differ in their cell cycle time and the number of divisions before they will become postmitotic (*id.*). The present patent application discloses this for adult human-derived cells (present application, p.18, ll 26-33). In addition, adult-derived human oligodendrocyte progenitor cells differentiate as oligodendrocytes and produce myelin much more quickly than do fetal or neonatal oligodendrocyte progenitor cells (Raff 1988). In particular, as reported in Nunes et al., "Identification and Isolation of Multipotential Neural Progenitor Cells from the Subcortical White Matter of the Adult Human Brain," *Nature Medicine* 9:439-447 (2003) ("Nunes 2003") (Evidence Appendix Exhibit 16) and Windrem 2004, adult-derived oligodendrocyte progenitor cells not only myelinate much more rapidly than do fetal oligodendrocyte progenitors, but they do so more efficiently, with a higher proportion exhibiting effective myelin production, and myelinating a greater number of neuronal axons per donor cell than their fetal-derived counterparts (First Rao Declaration ¶ 8). Adult cells are thus fundamentally more biased towards generating oligodendrocytes, maturing to express myelin proteins, and myelinating host axons (*id.*). Moreover, adult cells execute all of these functions and achieve each of these cellular milestones much more quickly than fetal cells (*id.*). As a result, they lend themselves to a very different set of

potential clinical targets than fetal or neonatal-derived progenitors, as reported in Roy et al., “Progenitor Cells of the Adult Human Subcortical White Matter,” In: *Myelin Biology and Disorders*, Vol. 1. R. Lazzarini, ed. Elsevier:Amsterdam, pp.259-287 (2004) (Evidence Appendix Exhibit 17) (*id.*).

Adult oligodendrocyte progenitor cells are thus fundamentally different from fetal or neonatal-derived progenitors. Therefore, the ’996 patent’s rat fetal oligodendrocyte-astrocyte precursor cells are very different from the adult oligodendrocyte progenitor cells in claim 26 of the present application (First Rao Declaration ¶ 8).

This argument was previously made in the prior appeal brief, p.18, ll 16-30, p.19, ll 1-18.

b). Claims 42-45

Appellants also maintain that claims 42-45 are patentable of their own accord, because these claims require that 66.3 ± 6.8% of cells in the enriched or purified preparation mature into O4-IR oligodendrocytes when cultured in the presence of 5% FBS/IGF-1. Nowhere is this feature taught by the ’996 patent. Indeed, as noted *supra*, the oligodendrocyte-astrocyte precursor cells of this reference produce mainly astrocytes.

This argument was presented in amendments filed on December 7, 2007, p.5, ll 2-10; March 14, 2008, p.5, ll 2-10; and October 27, 2008, p.5, ll 2-7.

7. <u>The ’996 Patent Does Not Render the Claimed Invention Obvious</u>

Having demonstrated that there is no basis for an anticipation rejection of claims 25, 26, and 29-41, the only prior art ground for rejection is obviousness under 35 U.S.C. § 103. However, this rejection also cannot stand.

35 U.S.C. § 103 imposes the requirement that an invention, to be patentable, must not have been obvious over the prior art “at the time the invention was made to a person having

ordinary skill in the art to which said subject matter pertains." A proper *prima facie* showing of obviousness requires the U.S. Patent and Trademark Office ("PTO") to satisfy three requirements. First, the prior art itself must suggest the desirability and, therefore, obviousness of a modification of a reference or the combination of references to achieve a claimed invention. *See Hodosh v. Block Drug Co. Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986); *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); *see also In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the PTO must show that, at the time the invention was made, the proposed modification had a reasonable expectation of success. *See Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Finally, the combination of references must teach or suggest each and every limitation of the claimed invention. *See In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Further, the question of obviousness should be analyzed in light of the holding of *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966) which sets forth the following factors for determining obviousness: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) such objective evidence of non-obviousness as commercial success, long felt but unresolved needs, and failure of others. *See also KSR International Co.. v. Teleflex, Inc.*, 550 U.S. 398, 405, 82 USPQ2d 1385, 1391 (2007). All evidence must be weighed before reaching a conclusion on obviousness under § 103. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1564, 1 USPQ2d 1593, 1594 (Fed. Cir. 1987); *Hodosh v. Block Drug*, 786 F.2d at 1143, 229 USPQ at 187-188.

In the Final Office Action (p.5, ll 16-21 to p.6, ll 1-2), the examiner makes the following statement on the issue of obviousness:

> One of ordinary skill in the art at the time of filing would have been motivated to use the methods taught by Rao et al. [(i.e. the '996 patent)] to isolate an enriched or purified preparation of human mitotic oligodendrocyte progenitor cells from humans so that these pure cell preparations could be used to treat neurological disorders in humans, such as Parkinson's Disease, such as by transplantation of such cells into an afflicted individual. This motivation is suggested by Rao et al. and the reasonable expectation of success comes from the results of Rao et al. who successfully isolated such an enriched or purified preparation of mitotic oligodendrocyte progenitor cells from rat.

However, at best, all that the '996 patent motivates those skilled in the art to do is find a preparation of bipotential oligodendrocyte-astrocyte precursor cells -- not oligodendrocyte-specified progenitor cells, as claimed by appellants. As noted above, there is absolutely no suggestion in the '996 patent that there are oligodendrocyte-specified progenitor cells in rats (or any other species), let alone any expectation of success in finding them. Without that teaching, why would anyone skilled in the art be motivated to look for such a cell type? Not only is the suggestion needed to motivate one skilled in the art to look for the claimed cell type missing from the '996 patent, but that reference teaches away from even thinking about doing so. Having investigated the issue of whether the $A2B5^+$ cells which generate oligodendrocytes and astrocytes in the '996 patent are multipotential or unipotential and having found (and taught) that they are multipotential, it is apparent that the '996 patent teaches away from the claimed invention. In view of this demotivating teaching, there is no basis for making an obviousness rejection. *See In re Fine,* 837 F.2d at 1074, 5 USPQ2d at 1598. This argument was made in the prior appeal brief, p.14, ll 6-36.

Given the ’996 patent’s clear teaching that its oligodendrocyte-astrocyte precursor cells have an astrocytic bias, it is not apparent how these cells can be regarded as the same as the claimed enriched or purified preparation from which a majority of the cells differentiate into O4 positive oligodendrocytes. In any event, the claims recite the conditions under which a majority of the cells in the enriched or purified preparation can mature into oligodendrocytes (i.e. cultured in PDGF, FGF2, and NT3 and then in the presence of 5% FBS/IGF-1). Since neither of these conditions, let alone the result that a majority of the cells of the enriched or purified preparation differentiate into O4 positive oligodendrocytes are taught by the ’996 patent, this reference can hardly be said to teach or render obvious the claimed invention. This argument was presented in amendments filed on December 7, 2007, p.8, ll 12-22; March 14, 2008, p.8, ll 12-22; October 27, 2008, p.8, ll 15-25; and September 10, 2009, p.8, ll 30-35, p.9, ll 1-6.

To the extent that the examiner’s rejection based on the inherent teachings of the ’996 patent is an obviousness rejection, it is inappropriate. In this regard, the following passage from *In re Rijckaert,* 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) is particularly instructive:

> ‘The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].’ ‘That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.’ Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection (citations omitted).

The examiner’s inherency position clearly fails to comport with this standard. This argument was previously made in the prior appeal brief, p.15, ll 1-14.

Even if the examiner had established a *prima facie* case of obviousness, which he has not, that obviousness case would be rebutted by the objective evidence of non-obviousness of record in this case. *See Tec Air, Inc. v. Denso Mfg. Mich. Inc.,* 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999).

The significance of appellants' present invention is apparent from the January 7, 2000, Research/Clinic Update for the National Multiple Sclerosis Society (Evidence Appendix Exhibit 18), which stated the following:

> Researchers at Cornell University Medical College, supported by the National MS Society, have for the first time isolated cells in the adult human brain that can divide and grow into myelin-making cells and that may ultimately be capable of replacing those damaged in multiple sclerosis.

The isolation of the adult human oligodendrocyte progenitor cell was thus chosen as one of the major MS-related discoveries of 1999 by the National Multiple Sclerosis Society. This work also merited a public affairs release of the Society for Neuroscience, which chose this discovery from thousands of annual research abstracts as one of its most important of the year, with an extensive and detailed release. A subsequent research summary by National MS Society (Evidence Appendix Exhibit 19) stated:

> Society-supported investigators at Cornell University Medical College reported, for the first time, being able to isolate immature ("progenitor") myelin-making cells in the adult human brain, remove them surgically and transform them, in laboratory dishes, into mature cells capable of making new myelin. This important step may provide a basis for new strategies for repairing damaged myelin in MS.

Appellants' work was reported in a number of both regional and national newspapers. An extensive report of appellants' work was reported in Newsday, then the largest circulation paper in New York City (Evidence Appendix Exhibit 20).

Both the significance and novelty of appellants' present invention are further apparent from its publication in the *Journal of Neuroscience* (first isolation of human oligodendrocyte progenitor cells: Roy et al., "Identification, Isolation, and Promoter-Defined Separation of Mitotic Oligodendrocyte Progenitor Cells from the Adult Human Subcortical White Matter," *J. Neuroscience* 19(22):9986-9995 (1999) (Evidence Appendix Exhibit 21); *Journal of Neuroscience Research* (first transplant of cells of human oligodendrocyte progenitor cells into demyelinated brain: Windrem et al., "Progenitor Cells Derived from the Adult Human Subcortical White Matter Disperse and Differentiate as Oligodendrocytes Within Demyelinated Lesions of the Rat Brain," *J. Neurosci. Res.* 69:966-975 (2002) (Evidence Appendix Exhibit 22) (*cover photo*)); *Nature Medicine* (first transplant of human oligodendrocyte progenitor cells into prenatal brain: Nunes 2003 (*cover photo*)); and again *Nature Medicine* (first transplantation of human oligodendrocyte progenitor cells into congenitally unmyelinated brain: Windrem 2004). These are among the pre-eminent journals in biomedicine. *Nature Medicine* currently has the highest impact factor of any journal in basic medical research, and its publication of work from the same laboratory twice in a year suggests the importance with which its editors view appellants' present invention and its uses. Thus, those skilled in the art recognized that the present invention was a substantial advance in the art over the '996 patent which did not report a means of isolating human oligodendrocyte-specified progenitor cells, let alone such progenitor cells themselves.

This argument was previously made in the prior appeal brief, p.15, l 1 to p.17, l 3.

C. Conclusion

For all the above reasons, the rejections under 35 U.S.C. §§ 112, 102, and 103 are improper and should be withdrawn.

Respectfully submitted,

Date: January 24, 2011

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VIII. CLAIMS APPENDIX

1-24. (Canceled).

25. (Rejected) An enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, wherein the majority of cells in the enriched or purified preparation differentiate into O4 positive oligodendrocytes, when cultured in PDGF, FGF2, and NT3, and further develop into galactocerebroside positive oligodendrocytes in the presence of 5% FBS/IGF-1, the mitotic oligodendrocyte progenitor cells are from a post-natal human, and a human cyclic nucleotide phosphodiesterase gene P2 promoter is transcriptionally active in the oligodendrocyte progenitor cells.

26. (Rejected) An enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, wherein the majority of cells in the enriched or purified preparation differentiate into O4 positive oligodendrocytes, when cultured in PDGF, FGF2, and NT3, and further develop into galactocerebroside positive oligodendrocytes in the presence of 5% FBS/IGF-1, the mitotic oligodendroctye progenitor cells are from an adult human, and a human cyclic nucleotide phosphodiesterase gene P2 promoter is transcriptionally active in the oligodendrocyte progenitor cells.

27-28. (Canceled).

29. (Rejected) An enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, wherein the majority of cells in the enriched or purified preparation differentiate into O4 positive oligodendrocytes, when cultured in PDGF, FGF2, and NT3, and further develop into galactocerebroside positive oligodendrocytes in the presence of 5% FBS/IGF-1, the oligodendrocyte progenitor cells express A2B5 antigen and do not express O4 antigen.

30. (Rejected) An enriched or purified preparation of human mitotic oligodendrocyte progenitor cells, wherein the majority of cells in the enriched or purified preparation differentiate into O4 positive oligodendrocytes, when cultured in PDGF, FGF2, and NT3, and further develop into galactocerebroside positive oligodendrocytes in the presence of 5% FBS/IGF-1, the mitotic oligodendrocyte progenitor cells are from a fetal human and a human cyclic nucleotide phosphodiesterase gene P2 promoter is transcriptionally active in the oligodendrocyte progenitor cells.

31. (Rejected) The enriched or purified preparation of claim 25, wherein the oligodendrocyte progenitor cells do not express GFAP antigen.

32. (Rejected) The enriched or purified preparation of claim 26, wherein the oligodendrocyte progenitor cells do not express GFAP antigen.

33. (Rejected) The enriched or purified preparation of claim 29, wherein the oligodendrocyte progenitor cells do not express GFAP antigen.

34. (Rejected) The enriched or purified preparation of claim 30, wherein the oligodendrocyte progenitor cells do not express GFAP antigen.

35. (Rejected) The enriched or purified preparation of claim 25, wherein the oligodendrocyte progenitor cells do not express βIII tubulin antigen.

36. (Rejected) The enriched or purified preparation of claim 26, wherein the oligodendrocyte progenitor cells do not express βIII tubulin antigen.

37. (Rejected) The enriched or purified preparation of claim 29, wherein the oligodendrocyte progenitor cells do not express βIII tubulin antigen.

38. (Rejected) The enriched or purified preparation of claim 30, wherein the oligodendrocyte progenitor cells do not express βIII tubulin antigen.

39. (Rejected) The enriched or purified preparation of claim 29, wherein the oligodendrocyte progenitor cells are from an adult human.

40. (Rejected) The enriched or purified preparation of claim 29, wherein the oligodendrocyte progenitor cells are from a fetal human.

41. (Rejected) The enriched or purified preparation of claim 29, wherein a human cyclic nucleotide phosphodiesterase gene P2 promoter is transcriptionally active in the oligodendrocyte progenitor cells.

42. (Rejected) The enriched or purified preparation of claim 25, wherein $66.3 \pm 6.8\%$ of cells in the enriched or purified preparation mature into O4-IR oligodendrocytes when cultured in the presence of 5% FBS/IGF-1.

43. (Rejected) The enriched or purified preparation of claim 26, wherein $66.3 \pm 6.8\%$ of cells in the enriched or purified preparation mature into O4-IR oligodendrocytes when cultured in the presence of 5% FBS/IGF-1.

44. (Rejected) The enriched or purified preparation of claim 29, wherein $66.3 \pm 6.8\%$ of cells in the enriched or purified preparation mature into O4-IR oligodendrocytes when cultured in the presence of 5% FBS/IGF-1.

45. (Canceled).

IX. EVIDENCE APPENDIX

EXHIBIT 1 – Declaration of Mahendra S. Rao, M.D., Ph.D. under 37 C.F.R. § 1.132

- Introduced into the record by appellant on October 21, 2004, and considered by the examiner in the office action, dated January 13, 2005.

EXHIBIT 2 – Second Declaration of Mahendra S. Rao, M.D., Ph.D. under 37 C.F.R. § 1.132

- Introduced into the record by appellant on May 25, 2005, and considered by the examiner in the office action, dated August 10, 2005.

EXHIBIT 3 – Gregori et al., "The Tripotential Glial-Restricted Precursor (GRP) Cell and Glial Development in the Spinal Cord: Generation of Bipotential Oligodendrocyte-Type-2 Astrocyte Progenitor Cells and Dorsal-Ventral Differences in GRP Cell Function," *J. Neurosci.* 22(1):248-256 (2002)

- Introduced by appellant on May 25, 2005, and considered by the examiner in the office action, dated August 10, 2005.

EXHIBIT 4 – Declaration of Steven A. Goldman under 37 C.F.R. § 1.132 ("First Goldman Declaration")

- Introduced by appellant on June 4, 2001, and considered by the examiner in the office action, dated August 28, 2001.

EXHIBIT 5 – Noble et al., "The O2A (Adult) Progenitor Cell: A Glial Stem Cell of the Adult Central Nervous System," *Seminars in Cell Biol.* 3:413-22 (1992)

- Introduced by appellant on December 18, 2003, and considered by the examiner in the office action, dated March 24, 2004.

EXHIBIT 6 - Windrem et al., "Fetal and Adult Human Oligodendrocyte Progenitor Cell Isolates Myelinate the Congenitally Dysmyelinated Brain," *Nature Medicine* 10:93-97 (2004)

- Introduced by appellant on October 21, 2004, and considered by the examiner in the office action, dated January 13, 2005.

EXHIBIT 7 – Third Declaration of Steven A. Goldman under 37 C.F.R. § 1.132

- Introduced by appellant on December 18, 2003, and considered by the examiner in the office action, dated March 24, 2004.

EXHIBIT 8 – Kirschenbaum et al., "*In Vitro* Neuronal Production and Differentiation by Precursor Cells Derived from the Adult Human Forebrain," *Cerebral Cortex* 6:576-89 (1994)

- Introduced by the PTO in the December 5, 2000, office action, to which appellant responded on June 4, 2001. Also presented by appellant on December 18, 2003, and considered by the examiner in the office action, dated March 24, 2004.

EXHIBIT 9 – Zhou et al., "The bHLH Transcription Factors OLIG2 and OLIG1 Couple Neuronal and Glial Subtype Specification," *Cell* 109:61-73 (2002)

- Introduced by appellant on May 25, 2005, and considered by the examiner in the office action, dated August 10, 2005.

EXHIBIT 10 – Vallstedt et al., "Multiple Dorsoventral Origins of Oligodendrocyte Generation in the Spinal Cord and Hindbrain," *Neuron* 45:55-67 (2005)

- Introduced by appellant on May 25, 2005, and considered by the examiner in the office action, dated August 10, 2005.

EXHIBIT 11 – Cai et al., "Generation of Oligodendrocyte Precursor Cells from Mouse Dorsal Spinal Cord Independent of *Nkx6* Regulation and *Shh* Signaling," *Neuron* 45:41-53 (2005)

- Introduced by appellant on May 25, 2005, and considered by the examiner in the office action, dated August 10, 2005.

EXHIBIT 12 – Pringle et al., "*Fgfr3* Expression by Astrocytes and Their Precursors: Evidence that Astrocytes and Oligodendrocytes Originate in Distinct Neuroepithelial Domains," *Development* 130:93-102 (2003)

- Introduced by appellant on May 25, 2005, and considered by the examiner in the office action, dated August 10, 2005.

EXHIBIT 13 – Yakovlev et al., "A Stochastic Model of Brain Cell Differentiation in Tissue Culture," *J. Math. Biol.* 37(1):49-60 (1998)

- Introduced by appellant on October 21, 2004, and considered by the examiner in the office action, dated January 13, 2005.

EXHIBIT 14 – Bögler et al., "Measurement of Time in Oligodendrocyte-Type-2 Astrocyte (O-2A) Progenitors is a Cellular Process Distinct from Differentiation or Division," *Dev. Biol.* 162(2):525-38 (1994)

- Introduced by appellant on October 21, 2004, and considered by the examiner in the office action, dated January 13, 2005.

EXHIBIT 15 – Raff et al., "Platelet-derived Growth Factor from Astrocytes Drives the Clock that Times Oligodendrocyte Development in Culture," *Nature* 333:562-65 (1988)

- Introduced by appellant on October 21, 2004, and considered by the examiner in the office action, dated January 13, 2005.

EXHIBIT 16 – Nunes et al., "Identification and Isolation of Multipotential Neural Progenitor Cells from the Subcortical White Matter of the Adult Human Brain," *Nature Medicine* 9:439-447 (2003)

- Introduced by appellant on October 21, 2004, and considered by the examiner in the office action, dated January 13, 2005.

EXHIBIT 17 – Roy et al., "Progenitor Cells of the Adult Human Subcortical White Matter," In: *Myelin Biology and Disorders*, Vol. 1. R. Lazzarini, ed. Elsevier:Amsterdam, pp.259-287 (2004)

- Introduced by appellant on October 21, 2004, and considered by the examiner in the office action, dated January 13, 2005.

EXHIBIT 18 – January 7, 2000, Research/Clinic Update for the National Multiple Sclerosis Society

- Introduced by appellant on December 18, 2003, and considered by the examiner in the office action, dated March 24, 2004.

EXHIBIT 19 – Summary of MS Research Progress – 1999, National MS Society, December 10, 1999

- Introduced by appellant on December 18, 2003, and considered by the examiner in the office action, dated March 24, 2004.

EXHIBIT 20 – "Beyond the Gray Area," Newsday Article, Jamie Talan

- Introduced by appellant on December 18, 2003, and considered by the examiner in the office action, dated March 24, 2004.

EXHIBIT 21 – Roy et al., "Identification, Isolation, and Promoter-Defined Separation of Mitotic Oligodendrocyte Progenitor Cells from the Adult Human Subcortical White Matter," *J. Neuroscience* 19(22):9986-9995 (1999)

- Introduced by appellant on December 18, 2003, and considered by the examiner in the office action, dated March 24, 2004.

EXHIBIT 22 – Windrem et al., "Progenitor Cells Derived from the Adult Human Subcortical White Matter Disperse and Differentiate as Oligodendrocytes Within Demyelinated Lesions of the Rat Brain," *J. Neurosci. Res.* 69:966-975 (2002)

- Introduced by appellant on December 18, 2003, and considered by the examiner in the office action, dated March 24, 2004.

X. RELATED PROCEEDINGS APPENDIX

Since the prior appeal occurred in this case, all papers relating to that appeal are of record in the prosecution file of this application and, therefore, need not be cited.